



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification <sup>6</sup> : <b>A61K 9/34</b></p>	<b>A1</b>	<p>(11) International Publication Number: <b>WO 99/48481</b></p> <p>(43) International Publication Date: 30 September 1999 (30.09.99)</p>		
<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; vertical-align: top; border: none; padding: 5px;"> <p>(21) International Application Number: PCT/US99/06339</p> <p>(22) International Filing Date: 23 March 1999 (23.03.99)</p> <p>(30) Priority Data: 09/047,863      25 March 1998 (25.03.98)      US</p> <p>(71) Applicant: TEMPLE UNIVERSITY OF THE COMMON-WEALTH SYSTEM OF HIGHER EDUCATION [US/US]; Broad Street and Montgomery Avenue, Philadelphia, PA 19122 (US).</p> <p>(72) Inventor: KIM, Cherng-ju; 132 Tudur Drive, North Wales, PA 19454 (US).</p> <p>(74) Agents: ANDERSEN, Robert, L. et al.; Ratner &amp; Prestia, 301, One Westlakes (Berwyn), P.O. Box 980, Valley Forge, PA 19482-0980 (US).</p> </td> <td style="width: 50%; vertical-align: top; border: none; padding: 5px;"> <p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b> <i>With international search report.</i></p> </td> </tr> </table>			<p>(21) International Application Number: PCT/US99/06339</p> <p>(22) International Filing Date: 23 March 1999 (23.03.99)</p> <p>(30) Priority Data: 09/047,863      25 March 1998 (25.03.98)      US</p> <p>(71) Applicant: TEMPLE UNIVERSITY OF THE COMMON-WEALTH SYSTEM OF HIGHER EDUCATION [US/US]; Broad Street and Montgomery Avenue, Philadelphia, PA 19122 (US).</p> <p>(72) Inventor: KIM, Cherng-ju; 132 Tudur Drive, North Wales, PA 19454 (US).</p> <p>(74) Agents: ANDERSEN, Robert, L. et al.; Ratner &amp; Prestia, 301, One Westlakes (Berwyn), P.O. Box 980, Valley Forge, PA 19482-0980 (US).</p>	<p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b> <i>With international search report.</i></p>
<p>(21) International Application Number: PCT/US99/06339</p> <p>(22) International Filing Date: 23 March 1999 (23.03.99)</p> <p>(30) Priority Data: 09/047,863      25 March 1998 (25.03.98)      US</p> <p>(71) Applicant: TEMPLE UNIVERSITY OF THE COMMON-WEALTH SYSTEM OF HIGHER EDUCATION [US/US]; Broad Street and Montgomery Avenue, Philadelphia, PA 19122 (US).</p> <p>(72) Inventor: KIM, Cherng-ju; 132 Tudur Drive, North Wales, PA 19454 (US).</p> <p>(74) Agents: ANDERSEN, Robert, L. et al.; Ratner &amp; Prestia, 301, One Westlakes (Berwyn), P.O. Box 980, Valley Forge, PA 19482-0980 (US).</p>	<p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b> <i>With international search report.</i></p>			
<p>(54) Title: COATED DONUT-SHAPED TABLETS WITH LONG-TERM PARABOLIC AND ZERO-ORDER RELEASE KINETICS</p> <div style="text-align: center; margin: 20px 0;"> </div>				
<p>(57) Abstract</p> <p>A tablet for the controlled release of an active pharmaceutical ingredient. The tablet comprises a core having a donut-like configuration with a cylindrical hole extending through the center of the core. The core of the body comprises at least one active pharmaceutical agent and at least one hydrophilic, water-soluble, polymeric carrier. The core is coated with a hydrophobic, water-insoluble material covering all of the core except that which is defined by the cylindrical hole. Also included is a method of preparing a tablet for the controlled release of an active ingredient. The method comprises the steps of blending an active pharmaceutical ingredient, a water-soluble hydrophilic, polymeric carrier, and optionally an excipient, to form a mix; compressing the mix; punching a tablet from the mix; coating the tablet in a water insoluble, hydrophobic coating, then drilling a hole through the coated tablet. A second embodiment of this method includes drilling a first hole through the tablet before coating the tablet, placing a rod through the first hole, dipping the tablet into the coating, and then removing the rod and drilling a second hole in the tablet which is larger than the first hole.</p>				

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakistan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

- 1 -

## COATED DONUT-SHAPED TABLETS WITH LONG-TERM PARABOLIC AND ZERO-ORDER RELEASE KINETICS

### FIELD OF INVENTION

This invention relates generally to drug releasing tablets. More  
5 specifically, this invention relates to tablets for delivering water-soluble drugs over a long  
period of time at a nearly constant rate.

### BACKGROUND OF THE INVENTION

A well known practice for storing, and later delivering, an active ingredient  
involves forming the matter into compact tablets from which the matter can later be  
10 dissociated or released. One such use involves drug delivery where the drug is  
administered orally (or otherwise) into an organic system. Particularly, diffusion-  
controlled matrix devices have received a great deal of attention for drug delivery systems  
in past years. One approach has been to use insoluble porous disc matrices, in which the  
drug is loaded into the matrix to an amount greater than its solubility limit in the  
15 dissolution medium. It has been found, however, that the rate of solute diffusion out of  
these tablets is not consistent over time. Often, the diffusion rate changes with the square  
root of time. In such cases, the amount of drug available at a biologic site of absorption  
decreases quickly as a function of time if the absorption rate is greater than the drug  
release from the matrix, as it often is with the systems of the past.

20 This problem is significant in view of the fact that it is often desirable to  
have a steady rate of drug delivery. More specifically, a parabolic or zero order release  
kinetic is often desirable where drug delivery is desired to be constant over a given time  
period.

25 With much of the prior art, as the dissolution occurs, the surface area (i.e.  
the interface), between the solvent and active agent changes with time. If this dissolution  
begins at the outside surface of a tablet, as dissolution progresses the surface area between  
the active agent and the solvent decreases. Where a coated tablet has been drilled with a  
hole to allow solvent and active agent to interface beginning in the area where the hole  
was drilled, the surface area between the solvent and the active agent increases with time

- 2 -

and thus the rate of dissolution increases with time. These problems continue to be the focus of attempts to achieve constant, or near constant, release of active agents into an organic body over time.

Simple monolithic tablets for extended release dosages have been fabricated  
5 by compressing a mixture of a water-insoluble polymer, a drug, and excipients. Such tablets may yield first-order kinetics or square-root-of-time kinetics. An inherent limitation of this type of monolithic matrix is the increase in diffusional length resistance over time due to the insolubility of the polymer.

#### SUMMARY OF INVENTION

10 The present invention provides a tablet for the controlled release of an active ingredient. The tablet comprises a body having a donut-like configuration with a cylindrical hole extending coaxially through the center of the body. The core material of the body comprises at least one active pharmaceutical agent and at least one hydrophilic, water-soluble, polymeric carrier. The core material is coated with a hydrophobic, water-  
15 insoluble material covering all of the core material except that which is defined by the cylindrical hole.

Also included in the present invention is a method of preparing a tablet for the controlled release of an active ingredient. The method comprises the steps of mixing an active pharmaceutical ingredient, a hydrophilic, water soluble, polymeric carrier, and  
20 optionally an excipient; compressing the mix; punching a tablet from the mix; coating the tablet, and drilling a hole in the center of the tablet.

A second embodiment of the method includes the extra steps of drilling a first hole through the tablet before it is coated, coating the drilled tablet, and then drilling the tablet a second time with a hole larger than the first drilled hole. This method allows  
25 the tablet to be placed onto a rod (through the first hole), and inserted into the coating material during the coating process. The second drilling is performed to insure that the inner exposed area is clear of all coating.

- 3 -

### BRIEF DESCRIPTION OF THE DRAWING

The invention is best understood from the following detailed description when read in connection with the accompanying drawing wherein:

FIG. 1 is a partial section view of a device according to the present  
5 invention;

FIG. 2 is a graph illustrating fractional release of active ingredient versus time for differing active ingredient loading amounts given as percentages of overall core material;

FIG. 3 is a graph illustrating fractional release of active ingredient versus  
10 time for differing active ingredient loading amounts given as percentages of overall core material;

FIG. 4 is a graph illustrating fractional release of active ingredient versus time for differing active ingredients in combination with differing polymers;

FIG. 5 is a graph illustrating fractional release of active ingredient versus  
15 time for differing polymers and for tablets having different hole sizes;

FIG. 6 is a graph illustrating fractional release of active ingredient for differing polymers and for differing mixing rates;

FIG. 7 is a graph illustrating fractional release of different drugs, in varying fractional amounts, versus time; and

FIG. 8 is a graph illustrating fractional release of different drugs, in  
20 varying fractional amounts, versus time.

### DETAILED DESCRIPTION OF INVENTION

This invention provides a controlled-release tablet and a method for its preparation. The tablet of this invention achieves nearly linear (zero-order), or parabolic  
25 release kinetics for delivering water-soluble drugs over a long period of time at a nearly constant rate. The device comprises a body having a donut-like configuration with a cylindrical hole extending coaxially through the center of the body. The core material of the body comprises at least one active pharmaceutical agent and at least one hydrophilic,

- 4 -

water-soluble, polymeric carrier. The core material is coated with a hydrophobic, water-insoluble material covering all of the core material except that which is defined by the cylindrical hole.

FIG. 1 is a partial section view of a device according to the present invention. Hole **110** extends through the center of the tablet. The core region **112** is comprised of an active pharmaceutical ingredient, a water soluble, hydrophilic, polymeric carrier, and, optionally, an excipient. Hydrophobic, water insoluble coating **114** is present everywhere on the outside surface of core region **112** except that surface of the core region **112** exposed to the hole **110**.

Also included in the present invention is a method of preparing the device for the controlled release of an active ingredient. The method comprises the steps of blending an active pharmaceutical ingredient and a water soluble, hydrophilic, polymeric carrier to form a mix; optionally adding an excipient; compressing the mix; punching a tablet from the mix; coating the tablet in a hydrophobic, water-insoluble material; and drilling a hole in the tablet.

A second embodiment of this method includes the additional steps of drilling a first hole through the tablet before it is coated, coating the drilled tablet, and then drilling the tablet a second time with a hole larger than the first drilled hole. This method allows the tablet to be placed on a rod (through the first drilled hole) and inserted into the coating material during the coating process. After coating, the rod is removed and the second drilling is performed to insure that the inner exposed area is clear of all coating material.

The experimental results discussed below demonstrate that erosion controlled, and swelling/erosion controlled, systems can provide zero-order release dosage forms provided a constant surface area for release is maintained during drug release. Hydrophilic, water-soluble, polymeric carriers having erosion controlled or swelling/erosion controlled properties generally furnish a short release time. Despite that fact, by constricting the surface area available for release, one can extend the release time while maintaining the erosion controlled, or swelling/erosion controlled, properties.

- 5 -

For purposes of this invention, "erosion" of the hydrophilic material is the same physical process as "dissolution" of the hydrophilic material into the solvent. Generally, however, in the interest of clarity with respect to discussion of this invention, the hydrophilic materials will "erode" out of the tablet and the drug will "dissolve" into the solvent.

An "erosion controlled" system is one in which the most significant factor on the overall release kinetics is the rate of erosion of the carrier out of the core. Some hydrophilic materials swell before eroding, and some even swell while eroding. In these two cases, overall release kinetics will be described as being swelling/erosion controlled. That is to say, in swelling/erosion controlled cases, the most significant factor on the overall release kinetics is the rate of swelling and erosion (taken together) of the hydrophilic material as it leaves the core of the device.

In general, for a tablet of given size, drug release is governed by both the dissolution of the drug and the erosion and/or swelling of the hydrophilic, polymeric carrier. At high drug loading, there is relatively less hydrophilic, polymeric carrier present than in the case of low drug loading. Thus, in the case of a high-drug loaded tablet, erosion and/or swelling effects of the hydrophilic, polymeric carrier have less of an impact than in the case of the low-drug loaded tablet where relatively more of the hydrophilic, polymeric carrier is present. This fact can be exploited, as it is in the present invention, to develop drug-release tablets which achieve the desired drug release rates.

Water soluble, hydrophilic, polymeric carriers referenced in regard to this invention are those which dissolve completely in water at 25°C within 24 hours. More particularly, those hydrophilic, polymeric carriers which are used herein as the hydrophilic, water-soluble component in the core material are those which, beginning as a flat, 500 mg tablet having an 11 mm diameter (and no hole), visibly completely dissolve in water at 25°C within 24 hours of being placed in the water.

Experimental procedures and the results of experiments performed according to those procedures are discussed below. The following table displays the materials used and, in some cases, select characteristics of the material.

- 6 -

Material	Particular Characteristics	Supplier
E3* Hydroxypropylmethyl-cellulose	N/A	Dow Chemical (Ann Arbor, MI)
E5* Hydroxypropylmethyl-cellulose	N/A	Dow Chemical (Ann Arbor, MI)
E15*Hydroxypropylmethyl-cellulose	N/A	Dow Chemical (Ann Arbor, MI)
Polyethylene Oxide	MW = 100,000; 200,000 and 300,000	Union Carbide Corp. (Summit, NJ)
Polyethylene Oxide	MW = 100,000; 200,000 and 300,000	Aldrich Chemical (Milwaukee, WI)
Polyethylene Glycol	MW = 8,000	Union Carbide Corp. (Summit, NJ)
Hydroxypropyl cellulose 99-EXF NF	MW = 80,000	Hercules, Inc. (Wilmington, DE)
Ethylcellulose	Viscosity = 22 centipoise in 5% 80/20 toluene/ethanol solution	Aldrich Chemical (Milwaukee, WI)
Theophylline	N/A	Knoll AG (Ludwigshafen, Germany)
Magnesium Stearate	N/A	Amend Chemical (Irvington, NJ)
Nicardipine HCl	N/A	Sigma Chemical (St. Louis, MO)
Diltiazem HCl	N/A	Sigma Chemical (St. Louis, MO)

\*These are Dow Chemical names which indicate that the viscosity for each polymer in a 2% aqueous solution at 20°C is 3, 5, and 15 centipoise, respectively.

#### Preparation of Tablets

First, the coated, donut-shaped tablets were prepared. A drug (or drug  
 5 substitute, for purposes of experimentation and calculation of diffusion rate), a hydrophilic polymer, and magnesium stearate (1 % by weight; in this experiment, the total tablet was 600 mg) were blended in a mortar and compressed to form cores using a Carver press (Carver, Inc., Wabash, IN) under a 6000 lbf compression force. A tablet punch was then



- 7 -

used on the cores to produce a tablet with a flat surface having a diameter of 12.6 mm (0.496 inches). A first central hole (3/32") was bored with a high speed drill bit.

The tablets were then coated by inserting a glass rod in the hole (3/32") and dipping and rolling the cores in an ethylcellulose/dichloroethane solution (5% by weight ethylcellulose). After coating and drying, the hole size (3/32") of the coated, donut-shaped tablet was enlarged to a second size by a high speed drill bit. The final size of the hole in these experiments was either 1/8 inch or 3/16 inch. The particular hole size is indicated in the discussion below. As a general matter, hole size can range anywhere within 1/32 inch and 1/2 inch, depending on performance requirements, and one skilled in the art could readily determine the appropriate diameter.

#### Testing Procedure

*In-vitro* release of the drug component of the core material from the coated, donut-shaped tablets was carried out by dissolving each tablet and measuring diffusion of the drug into a solvent. Here, each tablet obtained pursuant to the above defined procedure was dissolved in a solvent using the USP paddle procedure on a VanKel 8000 dissolution apparatus in distilled/de-ionized water at 37°C. The stirring rate was 100 rpm, unless otherwise noted. Diltiazem HCl, theophylline, and nicardipine HCl were chosen as model drugs. The release of diltiazem HCl, theophylline, and nicardipine HCl was monitored by an HP8252A diode-array spectrophotometer at 268 nm, 244 nm, and 360 nm, respectively.

#### Results and Discussion

FIG. 2 shows the effect of drug loading on the release of diltiazem HCl (solubility in water: 50%) from coated, donut-shaped tablets according to the present invention using HPMC E3 and E5 with a 3/16" hole. Coated, donut-shaped tablets (HPMC E5) with 39% by weight drug loading achieve the release of the drug at a constant rate up to 18 hours before leveling off to completion with little tailing.

"Tailing" refers to the asymptotic character of drug release as the drug is nearly completely gone from the source. In other words, the last small percentage of drug often takes a very long time to diffuse out of the matrix with respect to the first majority

- 8 -

of drug released. Long tailing means the asymptotic value is approached slowly with respect to a short tailing release where the asymptotic value is reached relatively quickly.

As illustrated in FIG. 2, there is no significant difference in drug release kinetics of the coated, donut-shaped tablets with a drug loading of 39%, 20%, and 10% by weight. For drug loadings greater than 39% by weight, the release of the drug becomes faster as drug loading increases. It appears that release profiles become parabolic at high drug loadings (59% and 49% by weight). At high loading, drug release is governed by the dissolution of the drug or a combination of drug dissolution and polymer erosion. However, as drug loading decreases, release kinetics become linear due to a change of the controlling mechanism of drug release from the coated, donut-shaped tablets. For a drug loading level of less than 45% by weight, drug release is governed primarily by the erosion of HPMC E5. The diffusion of a freely water soluble drug (diltiazem HCl) from this matrix, however, significantly contributed to the overall release kinetics. Thus, overall, substantially linear release kinetics are observed, as shown in FIG. 2. This is especially so for drug loadings at or below 39%, out to about 1000 minutes (16 hours and 40 minutes), where some tailing begins.

In most cases when zero-order release kinetics from monolithic matrix systems are desired, drug diffusion in a matrix is a disadvantage. However, drug diffusion in the matrix turns into an advantage in the case of coated, donut-shaped tablets for achieving zero-order release kinetics. The release of diltiazem HCl from coated, donut-shaped tablets based on HPMC E3, as presented in FIG. 3, shows parabolic profiles for drug loadings of 10% to 39% by weight because drug release is controlled by the erosion of the carrier.

The parabolic release kinetics from coated, donut-shaped tablets can be expressed by a heterogeneous erosion mechanism if the hydrophilic, water-soluble material is highly erodible. The drug release rate at time  $t$  from a coated, donut-shaped tablet, having an outer radius  $r_o$ , a central hole radius  $a$ , a tablet thickness  $L$ , and an initial drug concentration  $C_o$ , is expressed by:

$$\frac{dM_t}{dt} = 2\pi k_e rL \quad (1)$$

- 9 -

where  $M_t$  is the amount of drug released at time  $t$ ,  $k_e$  the erosion rate constant, and  $r$  the radius of the tablet at time  $t$ . The time dependent change of the tablet radius can be expressed by

$$r = a + \frac{k_e}{C_o} t \quad (2)$$

5 Integrating equation (1) following substitution of equation (2) yields:

$$\frac{M_t}{M_\infty} = \frac{\left(\frac{a + k_e}{C_o} t\right)^2 - a^2}{r_o^2 - a^2} \quad (3)$$

where  $M_\infty$  is the total amount of drug in the tablet. Release profiles of 59% and 49% by weight drug loaded coated, donut-shaped tablets (HPMC E5) shown in FIG. 2 can be represented well by equation (3) with  $\frac{k_e}{C_o}$  of 0.082 and 0.055 cm/hr, respectively. Values  
 10 for  $\frac{k_e}{C_o}$  for HPMC E3 tablets are 0.069, 0.052, and 0.041 cm/hr for 39%, 20% and 10% by weight drug loading, respectively. The release kinetics from HPMC E3 are dependent on drug loading because the erosion of HPMC E3 is enhanced by the faster absorption of water with higher drug loading.

The effect of drug solubility on the drug release from coated, donut-shaped  
 15 tablets (HPMC E3 and E5) is shown in FIG. 4. Even though drug solubility decreases from greater than 50% (diltiazem HCl) to 1% (theophylline), drug release profiles from coated, donut-shaped tablets of HPMC E5 are essentially superimposable. This suggests that even a drug of 1% solubility provides a significantly dissolved state of drug in the matrix, resulting in a contribution of drug diffusion to the overall release kinetics. When  
 20 drug solubility is 0.5% (nicardipine HCl) or less, a slight time lag at the early stage of release is observed followed by a linear release. Thus, the release of nicardipine HCl from HPMC E5 is governed largely as a function of the polymer erosion.

The release of drugs from coated, donut-shaped tablets using HPMC E3 is, however, greatly influenced by the solubility of the drugs, especially in the case where  
 25 parabolic release profiles are desired. As drug solubility increases, the absorption of

- 10 -

water becomes rapid, leading to a faster erosion of HPMC E3. When the perforated, coated tablets were fabricated with a water *insoluble* drug carrier (i.e. ethylcellulose) or a water soluble simple excipient (i.e. lactose), the solubility of the drugs greatly influenced the drug release from perforated, coated tablets. This is presumed to be a result of increased water presence inside the matrix with increased drug solubility.

All of the coated, donut-shaped tablets mentioned above have a 3/16" hole diameter. FIG. 5 illustrates the effect of the hole diameter on the release of diltiazem HCl from coated, donut-shaped tablets. The smaller hole diameter provides a larger annular thickness, resulting in a longer release time. The release profiles from coated, donut-shaped tablets of HPMC E5 are linear through 85-90% release with no severe tailing while parabolic release profiles are maintained for coated, donut-shaped tablets of HPMC E3. One can manipulate the total drug release time by controlling the hole size and outer diameter of coated, donut-shaped tablets. It is better, however, to use a smaller hole size to fabricate coated, donut-shaped tablets because there is an increased possibility of coating the central hole surface of larger holed tablets when a mass production technology (pan and fluidization coating) is used.

Another factor affecting solubility rates is agitation. Increasing the stirring rate influences the erosion of the hydrophilic, water-soluble carrier so that the release rate of drugs from the erodible matrices is facilitated. FIG. 6 displays the effect of the stirring rate on the release of diltiazem HCl from the coated, donut-shaped tablets (HPMC E3 and E5) with a 3/16" hole diameter. As the stirring rate is increased from 50 rpm to 150 rpm, the release rate of the drug increases. This suggests that the hydrodynamic condition in the central hole significantly influences the erosion of the hydrophilic, water-soluble, polymeric carrier and the diffusion of the drug. At a stirring rate of 150 rpm, the drug release profile from coated, donut-shaped tablets of HPMC E5 (39% by weight drug loading) becomes parabolic because the contribution of drug diffusion to the overall release kinetics is minimal compared to the erosion of the hydrophilic, water-soluble, polymeric carrier.

Drug release profiles from coated, donut-shaped tablets with a 3/16" hole size based on other erodible (soluble) carriers were also ascertained. Parabolic release

- 11 -

profiles for some hydrophilic, water-soluble, polymeric carriers have been observed. One can obtain parabolic release kinetics expressed by equation (3) when erosion or swelling/erosion controlled matrix systems are used. When 39% by weight drug loaded polyethylene oxide of  $M_w=300,000$  is used, the swelling of the polymer increased relative to the use of HPMC. As a result, the collapse of the hole (3/16") is encountered at about 40% release, leading to a prolonged linear release (48 hours). When drug loading was increased to 59% by weight in coated, donut-shaped tablets of polyethylene oxide, no collapse of the hole was observed because a smaller amount of polyethylene oxide was available to swell and fill the central hole.

The release of diltiazem HCl from coated, donut-shaped tablets of polyethylene oxide ( $M_w=300,000$ , 59% by weight drug loading) slightly deviated from parabolic release kinetics because the diffusion of the drug plays an increased role in the overall release kinetics relative to the case where HPMC was used. When HPMC E15 was used, a linear release profile was obtained with 59% by weight drug loading. When a water *insoluble* polymer was used as a drug carrier (i.e., ethylcellulose), a non-linear (and non-parabolic) release profile was obtained because drug diffusion in the matrix controlled the release kinetics. This illustrates that the selection of the erodible hydrophilic water-soluble, polymeric carrier will determine the release rate and total release time along with the shape of release profile (parabolic and linear) of a coated, donut-shaped tablet. In general, parabolic release profiles are obtained if  $k_e/C_o$  is larger than 0.038 cm/hr.

The following table illustrates erosion rate constants of coated, donut-shaped tablets according to the present invention. Referring to equation 2, one notices that as time changes, the rate of diffusion changes very little. This, again, empirically supports the proposition that the rates are nearly zero-order.

**Erosion rate constants ( $k_e/C_o$ ) of coated donut-shaped tablets**

Polymer	Drug	Loadin g %	Hole Size (inch)	Stirring Rate (rpm)	$k_e/C_o$ (cm/hr)
HPMC E3	diltiazem	10	3/16	100	0.041( $\pm 1.7$ %)
	diltiazem	20	3/16	100	0.051( $\pm 2.5$ )

- 12 -

Polymer	Drug	Loadin g %	Hole Size (inch)	Stirring Rate (rpm)	$k_c/C_o$ (cm/hr)
					%)
	diltiazem	39	3/16	50	0.065( $\pm 2.1$ %)
	diltiazem	39	3/16	100	0.069( $\pm 2.7$ %)
	diltiazem	39	3/16	150	0.111( $\pm 5.8$ %)
	diltiazem	39	1/8	100	0.050( $\pm 0.7$ %)
HPMC E5	diltiazem	39	3.16	150	0.054( $\pm 2.9$ %)
	diltiazem	49	3/16	100	0.055( $\pm 2.0$ %)
	diltiazem	59	3/16	100	0.082( $\pm 2.2$ %)
Polyethylene Glycol MW = 8,000	diltiazem	39	3/16	100	0.153( $\pm 3.4$ %)
Polyethylene Oxide MW = 100,000	diltiazem	39	3/16	100	0.054( $\pm 0.9$ %)
Polyethylene Oxide MW = 200,000	diltiazem	39	3/16	100	0.040( $\pm 0.8$ %)
Polyethylene Oxide MW = 300,000	diltiazem	59	3/16	100	0.025( $\pm 1.9$ %)
Hydroxypropyl Cellulose	diltiazem	39	3/16	100	0.038( $\pm 1.1$ %)
HPMC E3	theophylline	39	3/16	100	0.053( $\pm 2.6$ %)
	nicardipine	39	3/16	100	0.03( $\pm 1.2$ %)

FIGs. 7 and 8 illustrate fractional release of different drugs, in varying fractional amounts, versus time. More particularly, FIG. 7 shows the fractional release of

- 13 -

Procardia in HPMC E3 when Procardia is loaded in amounts of 30 mg, 60 mg, and 90 mg. Also shown is the fractional release over time of TUSP in HPMC E3 when TUSP is loaded to 90 mg. One can see that nearly linear release is achieved in these cases for release occurring up to 25 hours.

5                   FIG. 8 is shows the fractional release of Volmax and TUSP loaded in HPMC E3 versus time. In FIG. 8, eight (8) mg of Volmax was loaded and 8 mg of TUSP was loaded. Here, nearly linear release occurred for about the first 8 hours.

                  Although most examples have focused on the use of particular polymers as the hydrophilic water-soluble carrier, other polymeric materials may be used. One  
10                   example of such a polymeric, hydrophilic, water-soluble carrier is cyclodextrin, in any of its three forms ( $\alpha$ ,  $\beta$ ,  $\gamma$ ). One skilled in the art could readily determine other such hydrophilic, water-soluble, polymeric carriers. Several cyclodextrin derivatives, for example, could be used as the hydrophilic, water soluble, polymeric carrier material.

                  Although this invention has been described with reference to specific  
15                   embodiments thereof, it is understood that other embodiments and variations of the invention as described and exemplified may be made by those skilled in the art without departing from the true spirit of the invention. It is intended that the appended claims be construed to include all such embodiments and variations.

- 14 -

What is Claimed:

1. A tablet for the controlled release of a pharmaceutically active ingredient, said tablet comprising:

5 a donut-shaped core material with a cylindrical hole extending through the center of said core comprising at least one pharmaceutically active ingredient and at least one hydrophilic, water-soluble, polymeric carrier; and

a coating of hydrophobic, water-insoluble material covering all of said core except the surface of said core surrounding said cylindrical hole.

10 2. The tablet according to claim 1 wherein said hole has a diameter in the range of 1/32 to 1/2 inches.

3. The tablet of claim 1 wherein said coating is ethylcellulose.

15 4. The device of claim 1 wherein said hydrophilic, water-soluble, polymeric carrier is selected from the group consisting of: hydroxypropylmethylcellulose; polyethylene oxide; polyethylene glycol; hydroxypropyl cellulose; hydroxyethylcellulose; cyclodextrin; and cyclodextrin derivatives.

5. A method of preparing a tablet for the controlled release of a pharmaceutically active ingredient, the method comprising:

blending an active ingredient and a hydrophilic, water soluble polymeric carrier to form a mix; compressing said mix; punching a tablet from said mix;

20 coating said tablet with a hydrophobic, water-insoluble coating material; and drilling a hole in said tablet.

6. The method according to claim 5 wherein said hole has a diameter in the range of 1/32 to 1/2 inches.

25 7. The method according to claim 5 wherein said coating is ethylcellulose.

8. The method according to claim 5 wherein said hydrophilic, water-soluble, polymeric carrier is selected from the group consisting of:



- 15 -

hydroxypropylmethylcellulose; polyethylene oxide; polyethylene glycol; hydroxypropyl cellulose; cyclodextrin; and cyclodextrin derivatives.

9. The method according to claim 5 further comprising:  
drilling a first hole through said tablet before coating said tablet;  
5 coating said tablet in a hydrophobic, water-insoluble coating material; then  
re-drilling said hole to form a second hole in said tablet having a diameter larger than the  
diameter of said first hole.

10. The method according to claim 9 wherein said first hole has a  
diameter in the range of 1/32 to 3/8 inches.

10 11. The method according to claim 9 wherein said second hole has a  
diameter in the range of 1/32 to 1/2 inches.

12. The method according to claim 9 wherein said coating is  
ethylcellulose.

13. The method according to claim 9 wherein said hydrophilic, water-  
15 soluble, polymeric carrier is selected from the group consisting of:  
hydroxypropylmethylcellulose; polyethylene oxide; polyethylene glycol; hydroxypropyl  
cellulose; cyclodextrin; and cyclodextrin derivatives.

14. A tablet for the controlled release of a pharmaceutically active  
ingredient, said tablet comprising:

20 a core material with a hole extending through the center of said core  
comprising at least one pharmaceutically active ingredient and at least one hydrophilic,  
water-soluble, polymeric carrier; and

a coating of hydrophobic, water-insoluble material covering all of said core  
except the surface of said core surrounding said hole.

25 15. The tablet of claim 14 wherein said coating is ethylcellulose.

16. The device of claim 14 wherein said hydrophilic, water-soluble,  
polymeric carrier is selected from the group consisting of: hydroxypropylmethylcellulose;

- 16 -

polyethylene oxide; polyethylene glycol; hydroxypropyl cellulose; hydroxyethylcellulose; cyclodextrin; and cyclodextrin derivatives.

17. The tablet according to claim 14 wherein said hydrophilic, water-soluble, polymeric carrier is selected from the group consisting of:

5 hydroxypropylmethylcellulose; polyethylene oxide; polyethylene glycol; hydroxypropyl cellulose; cyclodextrin; and cyclodextrin derivatives.

18. The tablet according to claim 14 wherein said hole has a diameter in the range of 1/32 to 1/2 inches.

1 / 4

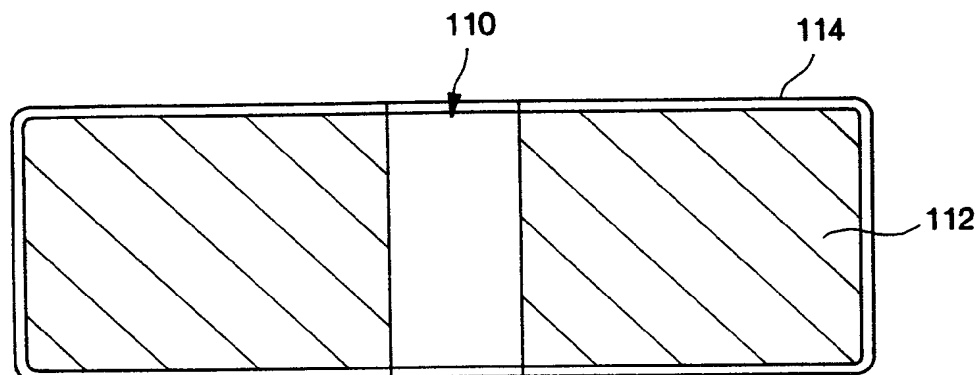


FIG. 1

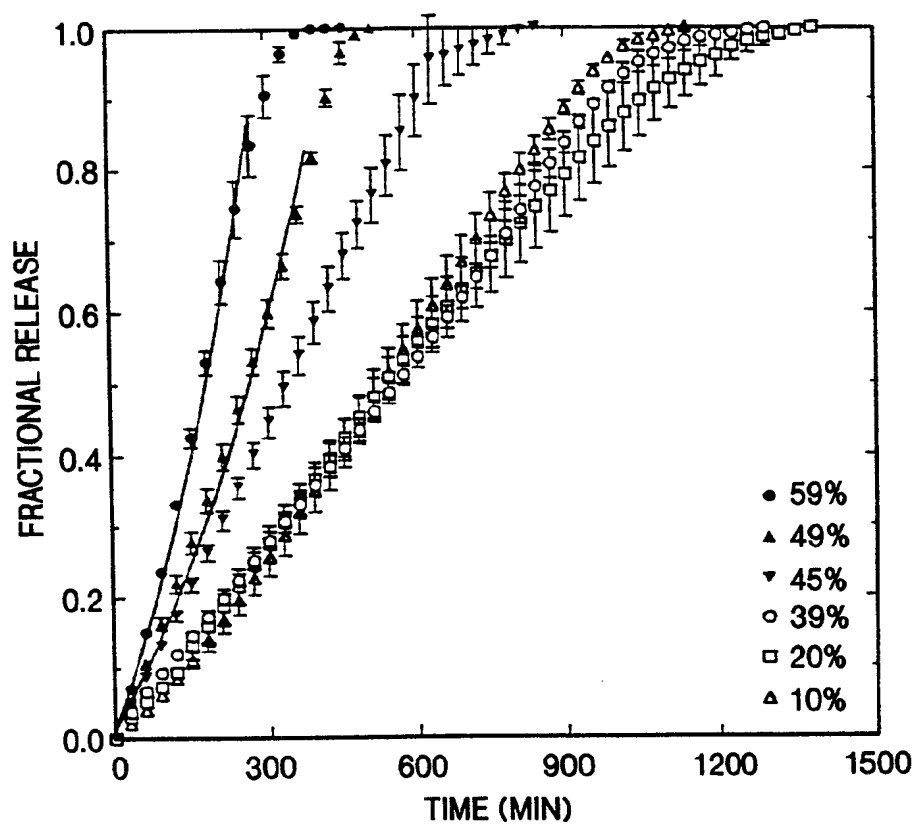


FIG. 2

2 / 4

FIG. 3

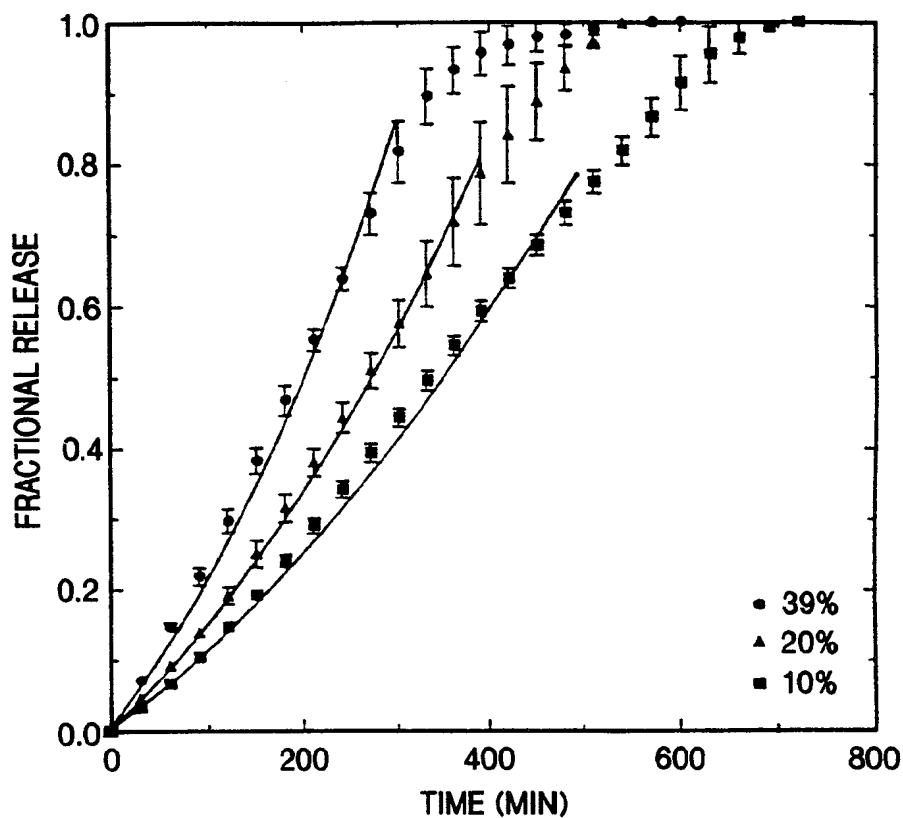
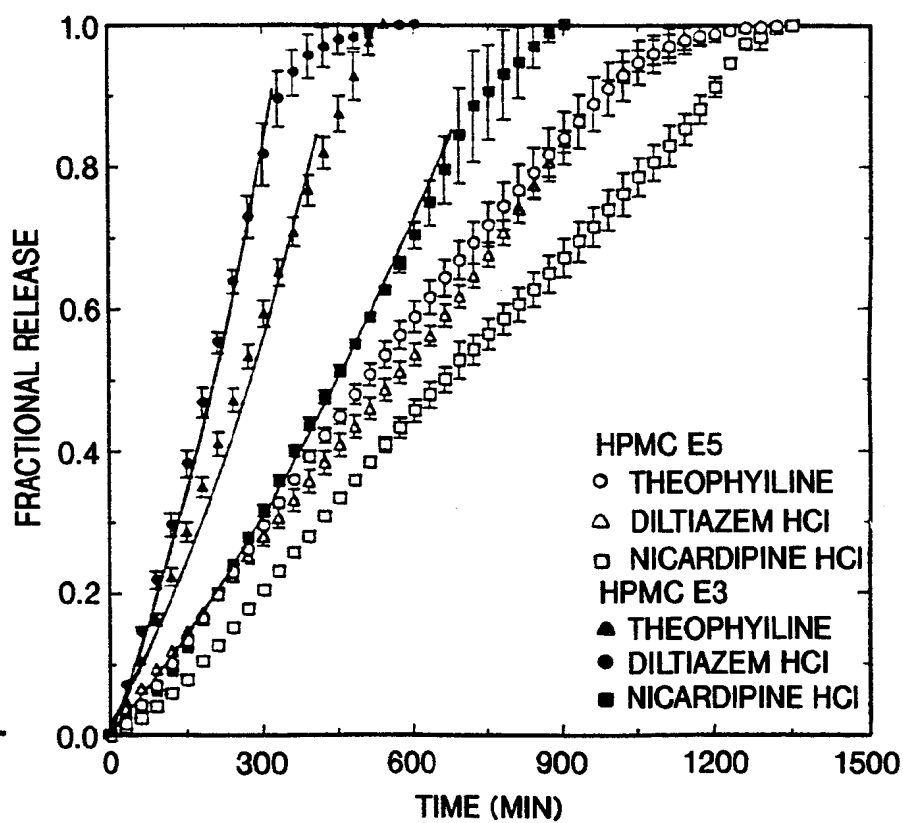


FIG. 4



SUBSTITUTE SHEET (RULE 26)

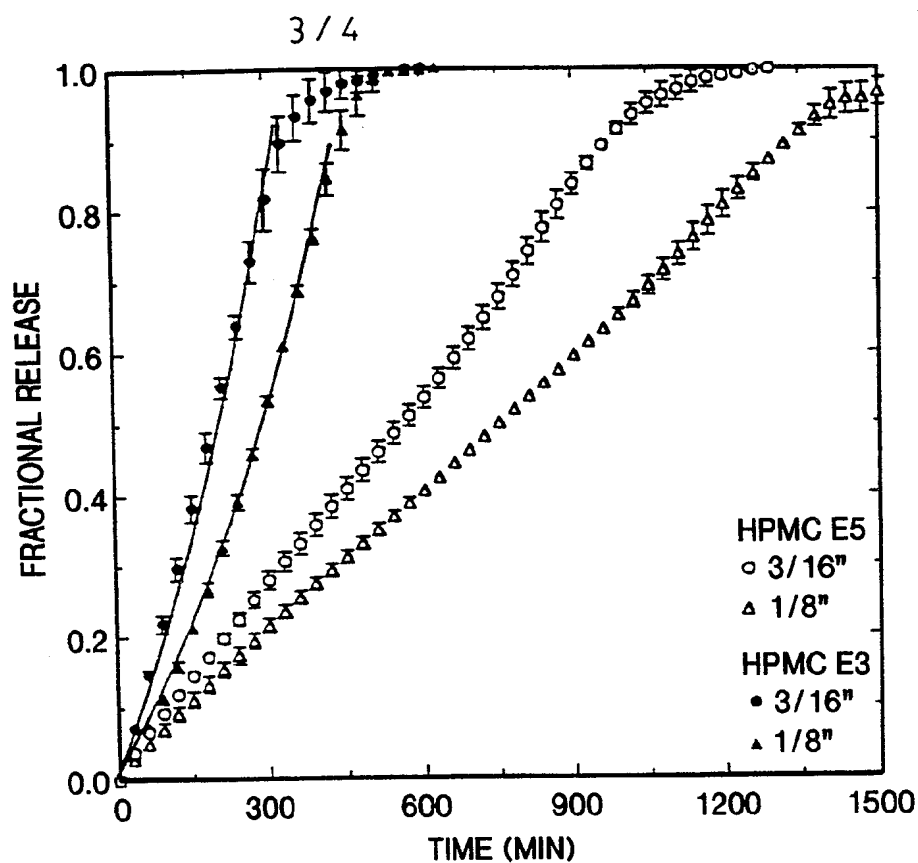


FIG. 5

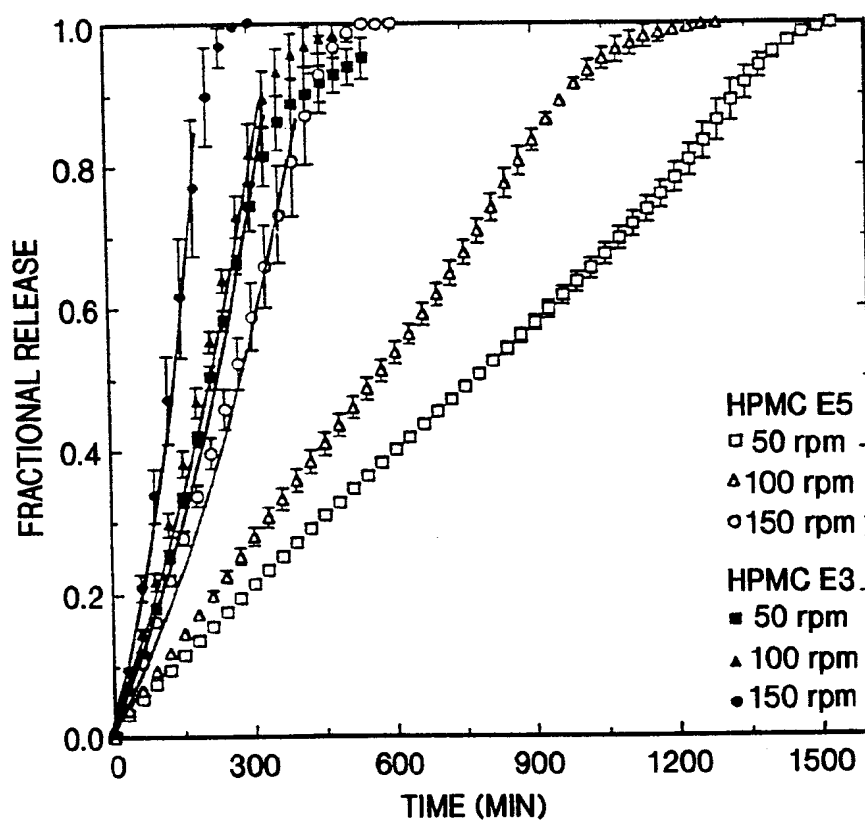
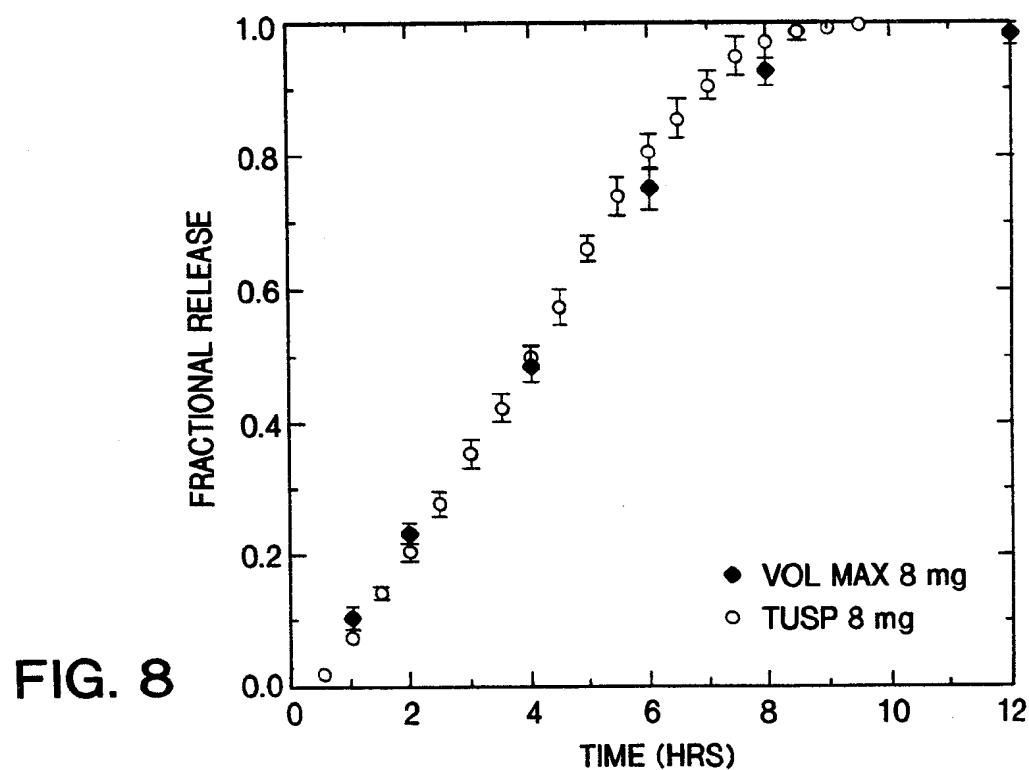
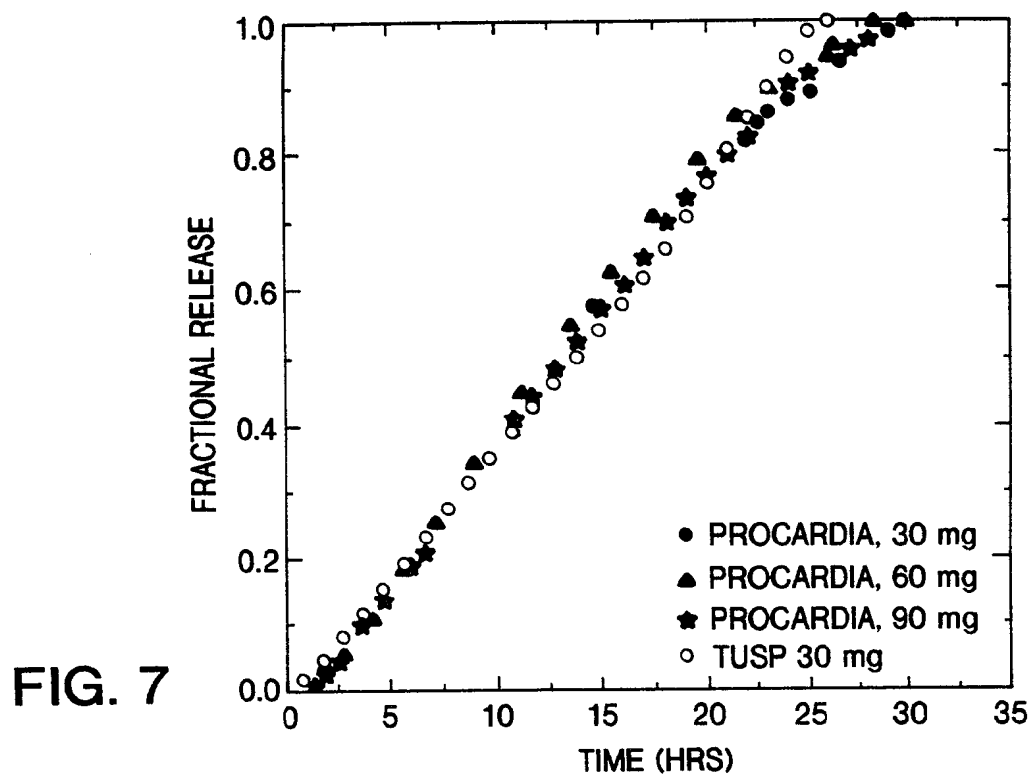


FIG. 6

4 / 4



## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US99/06339

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) : A61K 9/34

US CL : 424/475, 480

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/475, 480

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

NONE

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 4,816,262 A (McMULLEN) 28 March 1989, abstract, Figure 1 and columns 1-4.	1-2, 5-6, 14 & 17-18 ----- 3-4, 7-13 & 15-16
Y	KIM.C.J. Compressed Donut-shaped Tablets with Zero-Order Release Kinetics. Pharmaceutical Research. 1995, Vol. 12, No. 7, pages 1945-1948, especially pages 1045-1046.	1-18
Y	VANDELLI, M.A. et al. Selective coating of cylindrical matrices with a central hole. I. An interpretation of the swelling process. 1993, Vol. 100, pages 107-114, especially pages 107 and 109-114.	1-18



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*B* earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Z* document member of the same patent family
*O* document referring to an oral disclosure, use, exhibition or other means	
*P* document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

27 APRIL 1999

Date of mailing of the international search report

12 MAY 1999

Name and mailing address of the ISA/US  
Commissioner of Patents and Trademarks  
Box PCT  
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

GOLLAMUDI S KISHORE

Telephone No. (703) 308-1235